Second Cancer After Hodgkin's Disease—The Price of Success?

John D. Boice, Jr. *

The treatment of Hodgkin's disease is one of the triumphs of modern cancer therapy. Forty years ago, the average patient had a life expectancy of less than 3 years. Today, approximately three out of every four patients are curable *(1)*. This dramatic change in survival was made possible by the development of supervoltage x-ray therapy machines in the 1950s and 1960s and the subsequent introduction of combination chemotherapy. As a result of this phenomenal success, the long-term complications of treatment have assumed clinical importance. They include cardiopulmonary disease, sterility, thyroid dysfunction, altered immunity, and second cancer *(2)*.

By far the most serious consequence of curative therapies for Hodgkin's lymphoma is the heightened risk of developing a new cancer. Twenty years ago, secondary cancer was first recognized as a life-threatening effect of treatment *(3)*. Excess acute leukemia was observed early and was generally ascribed to chemotherapy. Non-Hodgkin's lymphoma was then reported to occur with increased frequency, probably as a result of disease-related or treatment-induced immunosuppression *(4)*. As patients survived for longer periods, solid tumors, thought to be radiation related, surpassed the hematologic malignancies in absolute terms as the major hazard of successful treatment. About one of every six patients with Hodgkin's disease is likely to develop a second cancer within 15 years of treatment *(5,6)*.

In this issue of the Journal, Hancock and colleagues *(7)* present convincing evidence that breast cancer is a serious complication of aggressive therapy for Hodgkin's disease. Among 885 women treated between 1961 and 1990 at Stanford University Medical Center, 25 patients developed breast cancer, whereas only about six cancers would have been expected on the basis of general population rates. All 25 patients had received radiotherapy that resulted in substantial exposure of breast tissue to radiation.

Overall, a threefold risk of breast cancer was apparent 5-9 years after treatment, increasing to more than 10-fold among 20-year survivors. There was a striking change in risk according to age at treatment, with no excess risk observed among the 300 women who were older than 30 years when they received irradiation. Otherwise, absolute risks were similar by age at exposure—three to four extra breast cancers per 1000 women per year.

Women treated under age 20, whose follow-up periods included ages with normally low breast cancer risk, were at much higher relative risk (RR) than women who were treated in their twenties. Radiation risk coefficients were calculated on the basis of the mantle dose, 40-47 Gy, which probably overestimates the actual dose to breast tissue. Nonetheless, the computed RR at 1 Gy (1.2-1.9) is similar to that observed in other studies of women exposed to ionizing radiation *(8)*. In the study by Hancock et al. *(7)*, there was a suggestion that chemotherapy with alkylating agents may have enhanced the breast cancer risk due to radiotherapy during the first 15 years after treatment. Death attributable to breast cancer was also significantly increased.

Radiotherapy was first used to treat Hodgkin's disease in 1902 *(9)*, but it was the pioneering studies at Stanford University Medical Center that formed the basis for prevailing views about the curability of this disease *(10)*. The present study from Stanford *(7)* carefully evaluates late complications of treatment and reinforces current understanding of radiation-induced breast cancer. Other than radiation dose, age at exposure is seen as the most important determinant of risk, with risk decreasing as age at exposure increases. Once the minimum 5-year latent period for radiation-induced solid tumors is passed, risk increases, perhaps to very high levels. The study by Hancock and associates *(7)* is the first to quantify the carcinogenic potential of very high radiation doses (>10 Gy) and raises the possibility that chemotherapy may have contributed to the high breast cancer risk. The value of careful surveillance was apparent in that more than half of the breast cancers were unknown to the patients and were detected during routine follow-up examinations.

Of special clinical interest is the finding that risk increased dramatically over time. For patients with more than 15 years of follow-up, the RR of breast cancer was

*See "Notes" section following "References."

greater than 10-fold, and the absolute risk was more than 15 extra cancers per 1000 women per year. If this level of risk continues throughout life, the majority of young women (under 30 years of age) successfully treated for Hodgkin's disease may eventually develop breast cancer. The overall risks among long-term survivors of Hodgkin's disease are much greater than those seen in other studies of women exposed to radiation *(8,11)* and point to the need for lifetime screening for the early detection and treatment of secondary breast cancer *(12)*.

The possible reasons why women successfully cured of Hodgkin's disease are at such high risk for breast cancer include the high radiation dose to breast tissue, the young age of patients with Hodgkin's disease, the concomitant influence of systemic chemotherapy (which may potentiate the effect of radiotherapy), the effect of a seriously impaired immune system (related to Hodgkin disease itself and/or its treatment), and the possibility of an underlying genetic susceptibility to environmental carcinogens.

It is somewhat surprising that doses greater than 10 Gy are associated with a breast cancer risk of the same magnitude per unit dose as that seen among populations exposed to much lower levels. Very high doses are more effective in killing cells than transforming them, and thus a lower risk might have been expected. Precise dosimetry is difficult because of the large dose gradient across the breast from mantle radiotherapy (3-44 Gy) and because of individual variations related to breast size, field position, and shielding with blocks *(13)*. More refined dosimetry, however, would only increase the radiogenic risk coefficients presented by the authors.

The decrease in radiation-related breast cancer with increasing age at exposure is consistent with the patterns reported in most other studies of women exposed to radiation, although an absence of risk among women exposed in their thirties is generally not seen *(11)*. In fact, because of the intense clinical follow-up afforded these patients, a slight excess risk due to screening alone might have been anticipated. Hodgkin's disease is characterized by a striking bimodality in incidence, with incidence peaks occurring in young adults (before age 30) and later in life *(10)*. Other than chance or possible differences in radiotherapy procedures or survival, it may be that intrinsic factors associated with the development of Hodgkin's disease at a young age contributed to the high risk of radiation-induced breast cancer among women who were under 30 when treated with radiation. Molecular studies might be informative if they could reveal genetic abnormalities of predictive importance [*cf., (14)*],

An important question is whether chemotherapy might contribute to the risk of solid tumors. Most second cancers among long-term survivors of Hodgkins disease have been ascribed to radiotherapy. Two recent studies *(6,15)*, however, have linked statistically significant increased risks of solid tumors, notably lung cancer, with chemotherapy. Studies of experimental animals *(16)* have associated mammary tumors with certain chemicals used in the treatment of Hodgkin's disease, such as doxorubicin, procarbazine, and dacarbazine. Hancock et al. *(7)* now raise the possibility that chemotherapy might have potentiated the carcinogenic effect of radiotherapy. Further follow-up of patients with Hodgkin's disease should reveal whether chemotherapy-related neoplasia will mimic the pattern seen for radiation-related cancers, i.e., an early risk of leukemia and a late risk of solid tumors. If so, then the full impact of late cancer sequelae has not yet been seen.

The sobering consequences of successful cancer therapies should not discourage their use but should encourage the continued development of better therapies with less toxicity. Most patients would agree that the possibility of developing a second cancer some 20 years or more in the future is to be preferred to nearly certain death within a few years if treatment is withheld. Hodgkin's disease treatment is an example of the double-edged sword of cancer therapies—the diseased cells are killed, but healthy cells are often transformed. The benefits of curative treatment for Hodgkin's disease, however, outweigh the risk of unfortunate late consequences.

References

(1) Rosenberg SA: Hodgkin's disease: Challenges for the future. Cancer Res 49:767–769, 1989

(2) Young RC, Bookman MA, Longo DL: Late complications of Hodgkin's disease management. Monogr Natl Cancer Inst 10:55–60, 1990

(3) Arseneau JC, Sponzo RW, Levin DL, et al: Nonlymphomatous malignant tumors complicating Hodgkin's disease. Possible association with intensive therapy. N Engl J Med 287:1119–1122, 1972

(4) Krikorian JG, Burke JS, Rosenberg SA, et al: Occurrence of non-Hodgkin's lymphoma after therapy for Hodgkin's disease. N Engl J Med 300:452–458, 1979

(5) Tucker MA, Coleman CN, Cox RS, et al: Risk of second cancers after treatment for Hodgkin's disease. N Engl J Med 318:76–81, 1988

(6) Swerdlow AJ, Douglas AJ, Hudson GV, et al: Risk of second primary cancers after Hodgkin's disease by type of treatment: Analysis of 2846 patients in the British National Lymphoma Investigation. BMJ 304:1137–1143, 1992

(7) Hancock SL, Tucker MA, Hoppe RT: Breast cancer after treatment of Hodgkin's disease. J Natl Cancer Inst 85:25–31, 1993

(8) Boice JD Jr, Preston D, Davis FG, et al: Frequent chest x-ray fluoroscopy and breast cancer incidence among tuberculosis patients in Massachusetts. Radiat Res 125:214–222, 1991

(9) Pusey WA: Cases of sarcoma and of Hodgkin's disease treated by exposures to x-rays: A preliminary report. JAMA 38:166–l70, 1902

(10) Hellman S, Jaffee ES, DeVita VT Jr: Hodgkin's disease. *In* Cancer: Principles and Practice of Oncology (DeVita VT Jr, Hellman S, Rosenberg SA, eds). Philadelphia: Lippincott, 1989, pp 1696–1740

(11) Committee on the Biological Effects of Ionizing Radiations, National Research Council: Health effects of exposure to low levels of ionizing radiation. BEIR V. Washington, DC: Natl Acad Press, 1990

(12) Dershaw DD, Yahalom J, Petrek JA: Breast carcinoma in women previously treated for Hodgkin's disease: Mammographic evaluation. Radiology 184:421–423, 1992

(13) Zellmer DL, Wilson JF, Janjan NA: Dosimetry of the breast for determining carcinogenic risk in mantle irradiation. Int J Radiat Oncol Biol Phys 21:1343–1351, 1991

(14) Li FP, Garber JE, Friend SH, et al: Recommendations on predictive testing for germ line p53 mutations among cancer-prone individuals. J Natl Cancer Inst 84:1156–l160, 1992

(15) Kaldor JM, Day NE, Bell J, et al: Lung cancer following Hodgkin's disease: A case-control study. Int J Cancer 52:677–681, 1992

(16) IARC Monographs on the Evaluation of the Carcinogenic Risk of Chemicals to Humans, Suppl 4. Lyon: International Agency for Research on Cancer, 1982, pp 29–31, 103–104, 220–221

Notes

Correspondence to: John D. Boice, Jr., Sc.D., Radiation Epidemiology Branch, Division of Cancer Etiology, National Cancer Institute, National Institutes of Health, 6130 Executive Blvd., Executive Plaza North, Rm. 408, Rockville, MD 20852.

Manuscript received December 2, 1992; accepted December 8, 1992.